Cyclotryptophan Mycotoxins: Short Synthesis of the Desymmetrized *meso*-Chimonantine Core of Leptosin C

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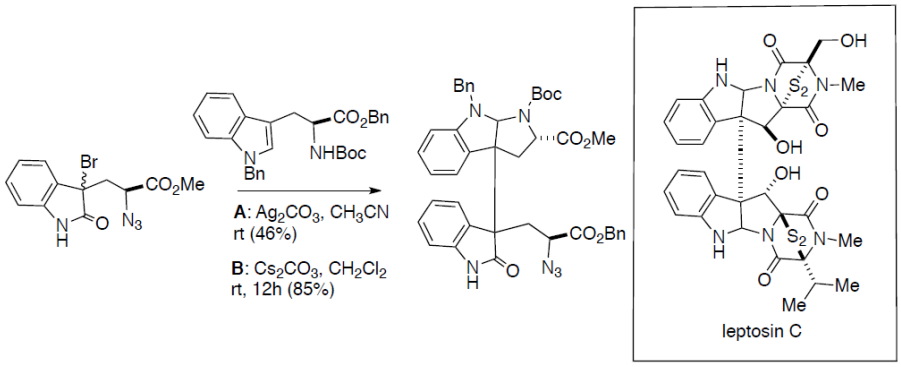
Dedicated to Professor Dieter Enders on the occasion of his 70th birthday.



Abstract: The desymmetrized *meso*-chimonantine core of leptosin C was prepared in a stereoselective convergent sequence in 5 steps as the longest linear path from methyl L-tryptophane HCl as starting material. The key step of this approach was the *meso*-selective [4+2] cycloaddition between the bromooxindole and tryptophane derivatives allowing to define the adjacent quaternary benzylic centers in a high diastereoselectivity and chemical yield.

Key words: asymmetric synthesis; mycotoxins; alkaloids; cycloadditions, tandem reaction.

Epi(polythio)diketopiperazine (ETP) alkaloids constitute a large and diverse family of natural products produced as secondary metabolites by a number of filamentous fungi and have received substantial attention from the scientific community in the last years due to their potent biological activity and complex molecular architecture.[2,3] The largest number of natural ETP mycotoxins is derived either from phenylalanine, or, from tryptophan and contains an ETP ring fused to a cyclotryptophan, or, cyclotryptamine fragment. They are characterized by a monomer or « dimer » structure in which the symmetry is often broken by differences in the substitution pattern, or, by the stereochemistry of identic functions of the two half of the natural product (Figure 1). They display a broad spectrum of biological properties,[1,2,4] including antibacterial, anticancer, antiviral, antiparasitic, antifungal, antimalarial, immunosuppressive and anti-inflammatory activities, among others. Recently, it has also been reported that they inhibit a variety of cellular targets and signaling processes critical for cancer cell growth,[5] suggesting that ETPs may have utility as lead molecules for drug development and molecular tools.[6] Among the most potent heterodimeric epi(polythio)diketopiperazines, polybispyrroloindoline alkaloids such as leptosins[7] and verticillins (gliocladins)[3] challenged chemists for decades by their complex molecular architecture paired with their complex and potent biological activity (Figure 1). The challenges posed by molecular structures with sterically congested stereogenic *vic* benzylic centers the highly acid-, base-, and redox-sensitive functional groups, inspired a number of elegant chemistry that culminated in a total synthesis of the (+)-11,11'-dideoxyverticillin A,[8] (+)-chaetocins A and C and (+)-12,12'-dideoxychetracin A[9] and motivated number of partial synthesis.[10]

While dimerization appears a plausible biosynthetic path, the detailed mechanism and in particular the nature of the precursors of the dimerization step are not fully elucidated.[3] The dimerization of *N*-methyltryptamine was suggested by May and Stoltz[11] as a general route to a number of related alkaloids (Scheme 1) including *meso*- and *d,l*-chimonantine derived alkaloids among which leptosins and verticillins, as well as glyocladins and chaetocins, differing essentially in the relative stereochemistry of the C(3) and C(3)' *vic* benzylic centers of the chimonantine core: leptosins have *meso* while natural verticillins have *d*/(+) configuration.

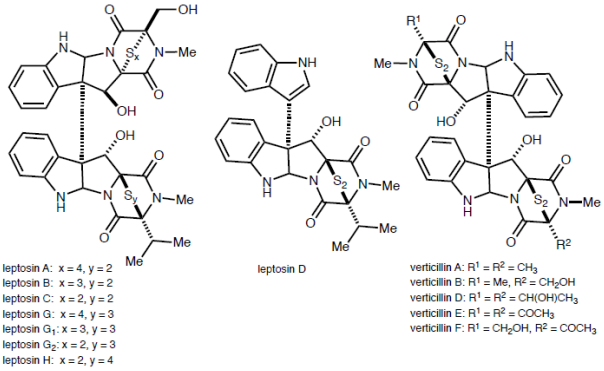
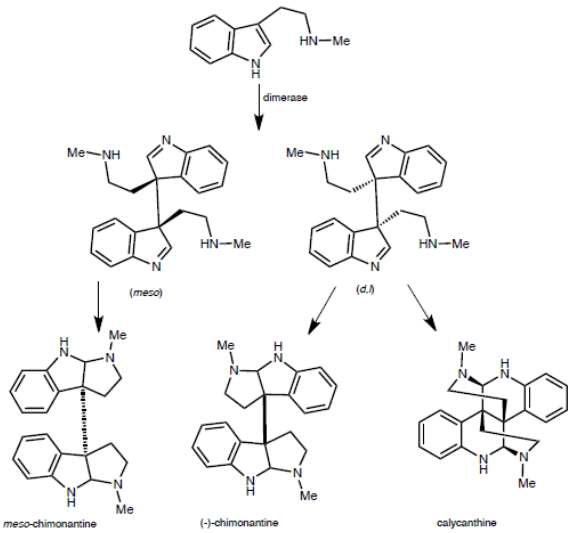


Figure 1. Selected cyclotryptophan*epi*(polythio)diketopiperazine (ETP) alkaloids.

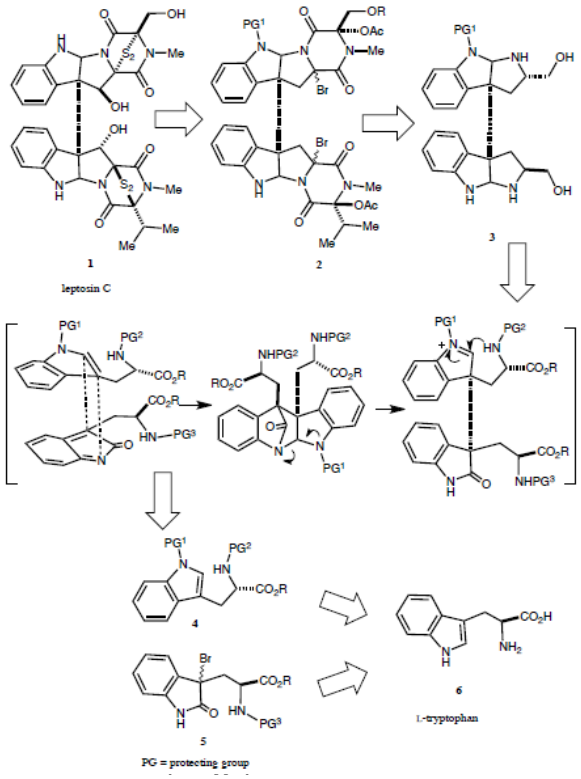


Scheme 1. The May-Stoltz biosynthesis of chimonanthine / calycanthine and related alkaloids.

Leptosins and verticillins bear also condensed diketopiperazine cycles[15] formed with serine, or, valine, or less frequently with alanine, or threonine, and being substituted usually by an epipolysulfanyl bridge.

Leptosins are formed as secondary metabolites produced by diverse terrestrial and marine fungus such as *Leptosphaeria* sp., originally separated from the marine alga *Sargassum tortile.*[12] Leptosins have great structural diversity: the symmetric, heterodimer or more complex dissymmetric natural products have a rich and versatile biological activity. Leptosin C is a powerful and selective topoisomerase I inhibitor under *in vitro* as well as *in vivo* conditions;[13] it has 10 asymmetric centers, 6 of them are quaternary[14] and is substituted by hydroxyl at the C(11) and C(11)' positions of the chimonantine ring, adjacent to the quaternary carbon stereocenter. Structural variations within heterodimer leptosins concerns the substitution pattern of the diketoptperazine cycle, the sterochemistry of the C(11) centers and the length of the epipolysulfanyl bridge, as mono-, di-, tri- and tetrasulfide members are present in nature (NB: disulfides are the most prevalent).[15] While the epipolysulfanylbridge is necessary for the potent biological activity, the length (S_n) seems having only minor impact: it can inactivate proteins *via* reaction with thiol groups of cysteine residues, generating reactive oxygen species by redox cycling mechanism,[16] or, may sequester zinc from protein targets.[17] As far as we know, only one total synthesis of leptosin class compounds was reported (leptosin D) bearing only a unit of ETP and a 3-substituted indole moiety.[18]

Despite the structural similarity, the synthesis of *meso* and *d/l* chimonantine-type alkaloids presents different challenges: as the bio-inspired dimerization favors the formation of the (*d/l*) isomer leading preferentially to verticillin-type products, this strategy is difficultly applicable for the synthesis of leptosins. In our continuous interest in the synthesis of chimonantine alkaloids we were intrigued whether the [4+2] cycloaddition strategy, used in the synthesis of N_b-desmethyl-*meso*-chimonanthine can be applied for the

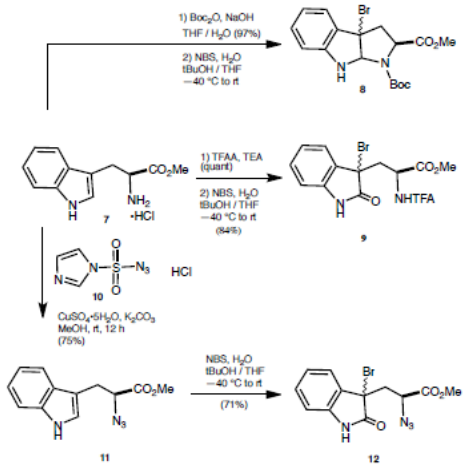


Scheme 2. Retrosynthetic analysis of leptosin C.

construction of the more densely substituted *meso*-chimonanthine core en route to leptosin C (Scheme 2). The key cycloaddition step was inspired by the elegant synthesis of (±)-perophoramidine developed by Fuchs and Funk in 2004[19] and consists of a diastereoselective tandem [4+2] inverse electron demand cycloaddition-cyclization of the tryptamine derivative **4** and bromooxindole **5**. According to our analysis compound **3** appeared suitable target *en route* to leptosin C that may provide opportunity for the construction of the desymmetrized 2,5-diketopiperazine cycles. Following the earlier strategies on ETP alkaloids, the introduction of the chemically labile disulfide bridge was left for the end of the synthesis.

Results and discussion

According to the retrosynthetic disconnection (Scheme 2), the desymmetrized *meso*-chimonantine derivative, **3**, having the carboxylate equivalents installed, appeared suitable primary synthetic target. The synthesis started with the preparation of the bromooxindole, **5,** key intermediate in the cycloaddition reaction. As the *N*-Boc derivative yielded the halocyclization product, **8** (Scheme 3), the corresponding trifluoroacetamide **9** was tested under bromooxidation, using NBS. The presence of dibrominated and non-brominated oxindoles was suppressed by maintaining the mixture at –40 °C under the addition step (84 %). Unfortunately, intermediate **9** appeared unsuitable for the cycloaddition as revealed instable in the presence of cesium carbonate, or, silver carbonate, without affording the desired product.

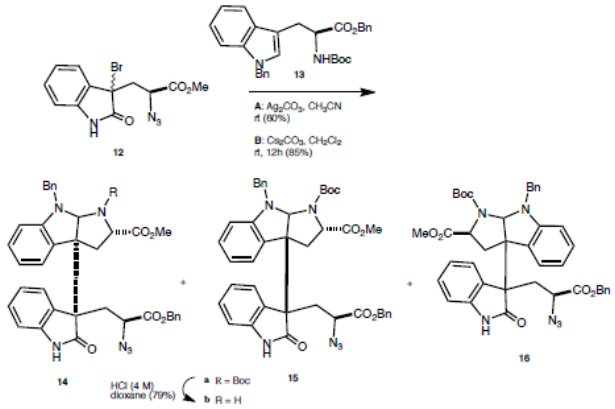


Scheme 3. Preparation of the diene precursor of the hetero-Diels-Alder reaction.

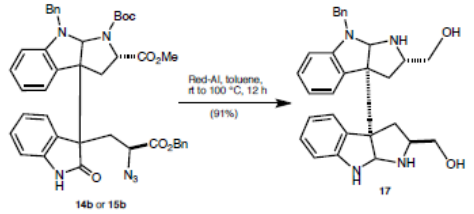
As a synthetic alternative, the amino ester salt, **7**,[20] was transformed to azide, **11**, under diazotransfer conditions[21] in the presence of imidazole-1-sulfonyl azide, **10** (75%, Scheme 3).[22,23,24] The azide group was selected as amine equivalent for its low nucleophilicity in the halooxidation step and also by the easy conversion to amine under the reductive cyclization conditions. While the hydrogen sulfate derivative of the azide transfer agent, **10**, was suggested as the safest on storage, the HCl derivative was preferred here, being more reactive. The oxidation was realized in the presence of NBS in aqueous *tert*-butanol, while the formation of non-brominated oxindole contamined invariably the mixture. This secondary reaction was easily eliminated by kept the temperature at −40 °C to rt, allowing to obtain **12** as a roughly 1:1 mixture of the two possible *meso* diastereomers in 71% isolated yield (Scheme 3). The mixture was used for the cycloaddition-cyclization reaction without separation.

The protected tryptophan **13** was obtained by following standard procedures.[25] As the one-pot doublebenzylation of the *N*-Boc-tryptophan in the presence of excess NaH and benzyl bromide resulted invariably, in a mixture of mono- and dibenzylated products,[26] the required dibenzylation was realized stepwise (see Experimental Part): the esterification of the carboxylate followed by *N*-benzylation of the indole moiety allowed to obtain the desired **13** in 48% overall yield, from the *N*-Boc protected tryptophan .

The cycloaddition-cyclization tandem was tested with bromooxindole **12** and benzyl ester **13** in the presence of stoichiometric amount of Cs_2CO_3, or Ag_2CO_3 (Scheme 4). When the cycloadditions was realized in the presence of silver carbonate (method A), 3 stereoisomers were obtained in 60% overall yield: two of them resulted from a high *meso*-selective cycloadditions, **14a** and **15a** in the ratio of 2/3 accompanied with a trace amount of *d/l* isomer as was deduced from the ^{1}H NMR spectra of the crude reaction mixture[27] (NB: both *meso* intermediates could be eventually used for the synthesis of the same target compound). When Cs_2CO_3, was used as base (method B), only the formation of the *meso* adducts, **14a** and **15a** were observed in 85% overall yield, although in a similar 2/3 selectivity. The diastereomers could be separated after the



Scheme 4. The *meso*-selective cycloaddition of bromooxindole 12 and indole 13.



Scheme 5. Synthesis of the *meso*-chimonantine core by reductive cyclization.

removal of the Boc protecting group by using HCl/dioxane (79%). The chimonantine core was assembled from the minor isomer in the presence of Red-Al in toluene (91%). The reductive conditions allowed the conversion of the azide to amine, promoted the reductive cyclization and also resulted in the conversion of the ester groups to hydroxymethylenes.

In conclusion, the desymmetrized and C(2)-functionnalized *meso*-chimonantine core **17** was prepared in a stereoselective convergent sequence in 5 steps as the longest linear sequence, from methyl L-tryptophane HCl, as starting material. The key step of this approach was the *meso*-selective [4+2] cycloaddition that was realized either by using Cs_2CO_3 base, or, by using Ag_2CO_3 allowing to define the adjacent quaternary benzyl centers in high *meso* selectivity. This highly convergent approach presents thus advantages in terms of diastereoselectivity, step number, and flexibility and may allow an easy entry to more complex desymmetrized bis-pyrroloindolinoindoline alkaloids, such as leptosin C.

Experimental section

General: Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 250 spectrometer (250 MHz and 63 MHz) and on a Bruker AV-500 spectrometer (500 MHz and 125 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent ($CDCl_3$: δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.16). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet), coupling constants in Hertz (Hz). All solvents and inorganic reagents were from commercial sources and used without purification unless otherwise noted. The Mass analyzer was a Micromass ZQ from Waters. The

capillary tension was 3.5 kV. The cone tension was 24 V. The temperature of the source was 130 °C and the temperature of desolvatation was 350 °C. Data were treated on Empower.

Procedures

(*S*)-Methyl 2-azido-3-(1H-indol-3-yl)propanoate (11)

3-Azidosulfonyl-3*H*-imidazol-2-ium hydrogen chloride[24] (4 g, 19.2 mmol) was added to the starting salt, **7** (4.1 g, 16 mmol), K_2CO_3 (4.4 g, 32 mmol), and $CuSO_4.5H_2O$ (10 µmg) in methanol (3 mL) and the mixture was stirred at room temperature for overnight. The mixture was then concentrated, diluted with H_2O (3 mL), acidified with HCl 6M to pH 1 and extracted with EtOAc (3×4 mL). The combined organic layers were dried over Na SO , filtered and concentrated. The crude was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1 to 1/1) to afford **11** in 75% as a colorless oil; $[\alpha]_D^{20} = -9.1$ (*c* 1.07, $CHCl_3$].

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.16 (bs, 1H), 7.71-7.61 (m, 1H), 7.39-7.33 (m, 1H), 7.30-7.14 (m, 2H), 7.07 (d, *J* = 2.5 Hz, 1H) , 4.24 (dd, *J* = 8.1, 5.5 Hz, 1H), 3.78 (*s*, 3H), 3.42 (dd, *J*=15.2, 5.9 Hz, 1H), 3.26 (dd, *J*=15.1, 7.7 Hz, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.8, 136.0, 126.9, 123.2, 122.1, 119.5, 118.2, 111.3, 109.7, 62.4, 52.5, 27.6.

HRMS: *m/z* $[M+Na]^+$calcd for $C_{12}H_{12}N_4O_2Na$: 267.0852, found: 267.0850.

General procedure for the bromooxydation of indoles

A solution of *N*-bromosuccinimide (2 equiv.) in THF (10 mL/mmol) was added to a solution of the starting compound (1 equiv), in *tert*-butanol (7mL/mmol), THF (10 mL/mmol) and H_2O (22 µL/mmol) at –40 ºC. The mixture was kept at 0 – 5 °C and stirred for 3 h. Concentrated under reduced pressure and the crude material was purified by flash column chromatography on silica gel.

(*S*)-Methyl 2-azido-3-(3-bromo-2-oxoindolin-3-yl)propanoate (12)

366 mg colorless foam of **12** was obtained from 488 mg of **11** (75 %); $[\alpha]_D^{20} = -55.9$ (*c* 2.16, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 9.84 (bs, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.33-7.21 (m, 1H), 7.13-6.95 (m, 2H), 3.66 (*s*, 3H), 3.56 (dd, *J* = 9.4 Hz, 1H), 3.04-2.93 (m, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm: 176.2, 169.2, 140.2, 130.7, 127.5, 124.4, 123.2, 111.4, 58.8, 53.5, 52.8, 39.6.

HRMS: *m/z* $[M+H]^+$ calcd for $C_{12}H_{12}N_4O_3Br$: 339.0087, found: 339.0080.

One-pot benzylation of *N*-Boc-L-tryptophan.

A flame-dried flask was cooled under a stream of nitrogen and charged with *N*-Boc-L-tryptophan[26] (1.40 g, 4.5 mmol) and DMF (4.5 mL). The resulting solution was cooled to 0 °C in an ice/water bath, and sodium hydride (60% dispersion in mineral oil, 540 mg, 13.5 mmol) was added. The resulting mixture was allowed to stir at 0 --- 5 °C for 30 min, and then benzyl bromide (1.92 mL, 16.2 mmol) was added dropwise. The reaction mixture was then stirred at rt until the starting material was consumed as followed by TLC analysis (36 h). The reaction was quenched with saturated aqueous NH_4Cl (10 mL), diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic layers were washed with brine (6×15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR analysis of the resulting yellow oil crude revealed the presence of mono and dibenzylated compounds, which were separated by flash chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 9/1 → 1/1).

(*S*)-Benzyl 2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoate[28]

To a solution of (S)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl) propanoate (2 g, 6.57 mmol) in DMF (27 mL) potassium carbonate (2.27 g, 16.5 mmol), and benzyl bromide (811 µl, 6.833 mmol) were added. The mixture was stirred at room temperature for 12h. The reaction was quenched with saturated aqueous NH_4Cl, diluted with EtOAc(10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic layers were washed with brine (3×15 mL), dried over anhydrous Na_2SO_4, filtrated, and concentrated in vacuo. A white powder was obtained after recrystallization from cyclohexane (81%). Spectroscopic data were consistent with the previously reported.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.00 (bs, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.38–7.30 (m, 4H), 7.29–7.17 (m, 3H), 7.16–7.07 (m, 1H), 6.81 (s, 1H), 5.09 (d, *J* = 3.7 Hz, 2H), 4.79–4.61 (m, 1H), 3.29 (d, *J* = 5.3 Hz, 2H), 1.43 (s, 9H).

(*S*)-Benzyl 3-(1-benzyl-1*H*-indol-3-yl)-2-((*tert*-butoxycarbonyl)ami-no)propanoate (13)[26]

To a solution of (*S*)-benzyl 2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoate (2 g, 5.07 mmol) in DMF (10 mL), NaH (0.507 g, 12.7 mmol) was added at 0–5°C. The mixture was stirred at the same temperature for 1 h. Then benzyl bromide (782 µL, 6.6 mmol) was added dropwise, and the reaction mixture was allowed to reach rt and stirred for 48 h. Quenched with saturated aqueous NH4Cl, diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL), the combined organic layers were washed with brine (3×15 mL), dried over anhydrous Na_2SO_4, filtrated, and concentrated in vacuo. The product was isolated by flash column chromatography on silica gel (eluents: cyclohexane/EtOAc 9/1 to 1/1). White solid (1.27 g, 59%). Spectroscopic data were consistent with the previously reported.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.8 Hz, 1H), 7.39–6.90 (m, 14H), 6.64 (bs, 1H), 5.12 (s, 2H), 5.09–4.95 (m, 2H), 4.75–4.58(m, 2H), 3.40–3.08 (m, 1H), 1.40 (s, 9H).

The tandem cycloaddition-cyclization reaction: 2-Benzyl 1-*tert*-butyl 3a-(3-((*S*)-2-azido-3-methoxy-3-oxopropyl)-2-oxoindolin-3-yl)-8-benzyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2*H*)-dicarboxylate (14a and **15a)**

Method A:

To a solution of **13** (0.532 g, 1.1 mmol) and **12** (0.338 g, 1 mmol) in dry acetonitrile (10 mL), Ag_2CO_3 (0.551 g, 2 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash column chromatography on silica gel (eluents: cyclohexane/EtOAc 9/1 to1/1), (60 %, yellow foam). $[\alpha]_D^{20}$= –37.7 (*c* 0.88, $CHCl_3$].

Method B

To a solution of the corresponding bromo derivative **12**(0.338 g, 1 mmol) and **13** (0.532 g, 1.1 mmol) in dry dichloromethane (10 mL/mmol), cesium carbonate (1.14 g, 3.5 equiv.) was added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (10 mL/mmol) and extracted with CH_2Cl_2 (3 x 10 mL/mmol), and the combined organic layers were washed with brine (10 mL/mmol), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified by flash column chromatography on silica gel (eluting with cyclohexane/ethyl acetate 9/1 → 1/1) to afford the corresponding compound. Compound **14a** and **15a** were obtained as a mixture of diastereomers (dr 2:3 determined by ^{1}H NMR (250 MHz); analysis on the crude mixture) after flash column chromatography. Yellow foam; 630mg (85%) ; $[\alpha]_D^{20}$ = –41.5 (*c* 1.09, $CHCl_3$].

Major diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.93 (bs, 1H), 7.65–6.52 (m, 18H), 5.89 (m, 7.9 Hz, 2H), 5.22 (s, 1H), 4.88–4.63 (m, 2H), 4.31–4.20 (m, 1H), 3.64 (s, 3H), 3.30–3.16 (m, 1H), 2.94–2.51 (m, 4H), 1.33 (s, 9H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 178.3, 171.5, 170.2, 170.2, 153.8, 151.9, 139.0, 135.3, 129.9, 128.9, 128.5, 128.3, 128.3, 128.1, 127.9, 127.1, 126.9, 126.2, 126.0, 124.9, 121.9, 117.3, 110.2, 107.7, 83.5, 80.7, 66.6, 62.0, 60.5, 58.8, 53.5, 52.7, 33.4, 27.7, 26.8.

HRMS: *m/z* [M+Na]$^+$ calcd for $C_{42}H_{42}N_6Na$: 765.3013, found: 765.3018.

Benzyl 3a-(3-((S)-2-azido-3-(benzyloxy)-3-oxopropyl)-2-oxoindolin-3-yl)-8-benzyl 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate(**14b** and **15b**)

HCl in dioxane (4 M, 100 equiv.) was added to the Boc-protected compounds. The reaction mixture was stirred at room temperature overnight then concentrated under reduced pressure. The title compound was prepared from a 2:3 mixture of **14a** and **15a** (0.94 g, 1.26 mmol) and the desired compound was obtained after flash column chromatography on silica gel (eluents cyclohexane/ ethyl acetate 6/1 → EtOAc) as a mixture of diastereomers (dr 2:3 determined by ^{1}H NMR (250 MHz) analysis on the crude mixture). Yellow foam, 0.64 g, 79%.

Major diastereomer: 380 mg (47%), colorless foam; $[\alpha]_D^{20} = -1.1$ (*c* 0.89, $CHCl_3$].

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.79 (bs, 1H), 7.46–6.96 (m, 12H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.84–6.72 (m, 1H), 6.64 (s, 3H), 6.01 (d, *J* = 7.8 Hz, 1H), 4.74–4.40 (m, 2H), 4.29 (d, *J* = 16.3 Hz, 1H), 4.08–3.91 (m, 2H), 3.69 (s, 1H), 3.65 (s, 3H), 3.31–3.16 (m, 1H), 3.04–2.86 (m, 1H), 2.83–2.43 (m, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 179.2, 173.6, 170.3, 152.2, 141.3, 138.2, 135.4, 129.8, 128.7, 128.5, 128.4, 128.3, 128.3, 128.2, 127.9, 126.8, 126.6, 126.6, 125.1, 122.26, 116.7, 110.2, 106.6, 84.4, 66.8, 61.2, 60.5, 59.0, 53.7, 52.7, 36.5, 34.3, 29.6.

HRMS: : *m/z* [M+H]$^+$ calcd for $C_{37}H_{35}N_6O_5$: 643.2663, found: 643.2648.

Minor diastereomer: 260 mg, (32%), colorless foam;$[\alpha]_D^{20} = -45.5$ (*c* 1.00, $CHCl_3$].

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.16 (bs, 1H), 7.45–7.23 (m, 7H), 7.19–6.97 (m, 5H), 6.90–6.78 (m, 2H), 6.71–6.56 (m, 3H), 6.08 (d, *J* = 7.9 Hz, 1H), 5.17 (dd, *J* = 15.8, 12.2 Hz 2H), 4.76 (s, 1H), 4.38–4.04 (m, 2H), 3.71 (s, 3H), 3.71–3.54 (m, 2H), 3.29–3.05 (m, 1H), 2.92–2.68 (m, 2H), 2.60–2.37 (m, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 178.1, 172.8, 170.2, 152.1, 140.6, 138.2, 135.4, 129.7, 129.5, 128.6, 128.4, 128.4, 128.3, 128.0, 126.8, 126.8, 126.7, 125.0, 124.5, 122.6, 116.8, 109.8, 105.9, 84.0, 66.9, 63.0, 59.4, 59.2, 54.0, 52.8, 39.9, 34.5, 26.9.

HRMS: *m/z* [M+H]$^+$ calcd for $C_{37}H_{35}N_6O_5$: 643.2663, found: 643.2657.

(8-Benzyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-2,2'-diyl)dimethanol (17)

A solution of the minor isomer (411 mg, 0.64 mmol) was dissolved in toluene (10 mL) and cooled to 0 - 5 °C. Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (65 wt % in toluene; 1.83 mL, 6.4 mmol) was added dropwise to the cooled mixture and the resulting solution was allowed then to warm to rt. Then, the mixture was warmed to 100 °C and the temperature was maintained at 100 °C for 24 h. After cooling to rt, the reaction was quenched with saturated aqueous sodium potassium tartrate (23 mL), diluted with ethyl acetate (46 mL), and stirred vigorously for 45 min. The mixture was then diluted with water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 99/1 → 4/1+ 1% Et_3N) and then was dissolved in CH_2Cl_2 and washed with brine to afford the title compound **17** as yellow oil. Yield: 271.8 mg, 91%, colorless foam. $[\alpha]_D^{20} = -41.4$ (*c* 0.07, $CHCl_3$].

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.30–6.99 (m, 6H), 6.92–6.42 (m, 5H), 6.32–6.04 (m, 2H), 4.49–4.05 (m, 2H), 3.74–3.61 (m, 1H), 3.62–3.38 (m, 2H), 3.30–3.03 (m, 3H), 2.98–2.68 (m, 3H), 2.66–2.46 (m, 1H), 2.38–1.96 (m, 3H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 138.2, 132.8, 128.8, 128.6, 128.4, 127.4, 127.0, 126.9, 126.7, 124.9, 124.0, 119.1, 119.0, 116.8, 109.1, 105.9, 84.8, 79.2, 64.4, 62.7, 62.6, 60.5, 58.2, 49.1, 47.7, 40.0, 29.6.

HRMS: *m/z* [M+H]$^+$ calcd for $C_{29}H_{33}N_4O_2$: 469.2598, found: 469.2589.

Supporting Information

There is NO further Supporting Information to be published.

Primary Data

There is NO Primary Data associated with this manuscript.

References

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